CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-488

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-488
Review number: 1
Serial number/date/type of submission: 000/4-13-2002/original submission
Information to sponsor: Yes (*) No ( )
Sponsor and/or agent: ATRIX Laboratories, Fort Collins, CO
Manufacturer for drug substance .
Drug product manufacturer: Atrix Laboratories, Inc.
Reviewer name: Krishan L. Raheja
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date:

Drug:

Proposed Trade name: , ELIGARD 30 (leuprolide acetate)
Generic name (list alphabetically): Leuprolide acetate for injectable suspension
Code name:
Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate
CAS registry number: 74381-53-6
Mole file number:
Molecular formula/molecular weight: $C_{59}H_{84}N_{16}O_{12}$. $C_2H_4O_2$/1269.48 Daltons
Structure: see NDA 21-343 review dated 3-22-2001

Ecipient:

Generic name: 1-methyl-2-pyrrolidone
Synonyms/codes: N-methylpyrrolidone
NMP
N-methylpyrrol
H-20417
CAS registry No.: 872-50-4
Molecular weight: 99.13

Structure: see NDA 21343 review dated 3-22-2001
Relevant INDs/NDAs/DMFs: INDs
NDA 21-343
DMF for leuprolide acetate; for poly (D,L-lactide) and its copolymers. t

Drug class: GnRH agonist

Indication: ELIGARD 30 is indicated in the palliative treatment of advanced prostate cancer

Clinical formulation: ELIGARD 30 is designed as a parenteral drug product that consists of a sterile syringe containing the —— active drug substance, leuprolide acetate, a sterile syringe containing the polymeric ATRIGEL Delivery System, and a sterile needle for injection. The ATRIGEL Delivery System is composed of poly (DL-lactide-co-glycolide) (PLG) dissolved in N-methyl-2-pyrrolidone (NMP). The drug product is mixed immediately before patient administration. The drug product is designed to deliver a nominal 30 mg of leuprolide acetate over a four-month period. The injection mass is approximately 500 mg.
As administered, it is a biodegradable polymeric formulation consisting of ~ % 75:25 Poly (DL-lacatide-co-glycolide) ~ % N-methyl-2-pyrrolidone and 6% leuprolide acetate.

The composition of Eligard 30 constituted drug product is shown in table below:

Component	Function	% w/w	Dose delivered Mg/unit
Leuprolide acetate	Active		30.0*
75:25 Poly(DL-lactide-co-glycolide)	Polymer		211.5
Zn-methyl-2-pyrrolidone	Liquid carrier		258.5
Total delivered amount: 500 mg/unit			

* 30.0 mg leuprolide acetate is equivalent to approximately 28.0 mg leuprolide freebase

Route of administration: Subcutaneous

Proposed use: 30 mg leuprolide acetate formulation (ELIGARD 30) is an injectable extended release subcutaneous formulation intended for one injection every 4 months for the palliative treatment of advanced prostate cancer.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Leuprolide acetate is a potent GnRH (LH-RH) agonist used clinically for the palliative treatment of advanced prostate cancer. Leuprolide acts by preventing pulsatile hypothalamic stimulation of adenohypolysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (<50 ng/dl in serum). As little as 1-mg leuprolide acetate administered daily or after administration of depot formulations at intervals of one month or longer has been demonstrated to achieve prolonged testosterone suppression.
Atrtix Laboratories has developed the Leuprogel 7.5 mg drug product (Eligard 7.5 mg), a sustained release one-month formulation of leuprolide acetate, for the palliative treatment of advanced prostate cancer, which was approved under NDA 21-343. Atrix Laboratories has also submitted a 3-month extended release formulation, which is being reviewed under NDA 21-379.

Safety evaluation: The safety of leuprolide acetate is well established as it has been approved By the FDA as leuprolide injection and Lupron Depot as leuprolide acetate depot suspension under various NDAs for the treatment of both malignant and benign conditions. Lupron injection is approved for the palliative treatment of advanced prostate cancer and for the treatment of precocious puberty. Lupron Depot 3.75 mg is approved for the treatment of endometriosis. Lupron Depot 7.5 mg and Lupron Depot 22.5 mg for the palliative treatment of prostate cancer, and Lupron Depot-PD 7.5, 11.5 and 15 mg for the treatment of children with central precocious puberty. Atrix Laboratories Aligard 7.5 mg, a sustained release formulation of leuprolide acetate is approved for the palliative treatment of advanced prostate cancer and Eligard 22.5mg, a 3-month formulation for the same indication is being reviewed under NDA 21-379.

Safety issues relevant to clinical use: There are no safety issues for the proposed Eligard 30 mg leuprolide acetate, 4-month formulation as its composition is similar to that for the Aligard 7.5 mg (approved) and Eligard 22.5 mg formulation (under review) as shown in table below:

Formulation	Eligard 30 mg	Eligard 22.5 mg	Eligard 7.5 mg
Frequency of Administration	Once every Four months	Once every Three months	Once per Month
Active drug (Dose)	Leuprolide Acetate (30 mg)	Leuprolide Acetate (22.5 mg)	Leuprolide Acetate (7.5 mg)
Drug loading	6%	6%	3%
Polymer type (lactide/glycolide ratio)	PLG (75/25)	PLG (75/25)	PLGH (50/50)
Polymer mol.wt	15-24 kD	15-24 kD	23-45 kD
Solvent (%by wt.)	NMP (7%)	NMP (%)	NMP (%)
Injection volume	0.500 ml	0.375 ml	0.250 ml

Thus the components of 4-month and 3-month formulations are qualitatively similar to those of 1-month SC for formulation. The copolymer used in the 1-month formulation has a different ratio of lactide/glycolide subunits and a different mean molecular weight to achieve the drug release rate required for once monthly treatment.

Other clinically relevant issues:

Conclusions: Based on the safety of Eligard 7.5 mg approved under NDA 21-343 and the compositional and therapeutic similarities between the Eligard 7.5 mg and Eligard 30 mg formulations, there is no safety concern.

Communication review:

Labeling review: Label is similar to that for ATRIX Aligard 7.5 mg under NDA 21-343.

RECOMMENDATIONS: Based on the composition and therapeutic similarities of Aligard 30 mg with that of approved Eligard 7.5 mg formulation, Pharmacology recommends approval of Eligard 30 mg under NDA 21-488 for the palliative treatment of advanced prostate cancer.

Internal comments:

External recommendations (to sponsor): The sponsor should be informed as follows:

"There is sufficient published pre-clinical data to support safety of Eligard 30 mg for the palliative treatment of advanced prostate cancer. Carcinogenicity studies in rodents will be needed to support non-malignant related indications".

Draft letter content for sponsor (if not same as above):

NDA issues: none

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc:
original NDA 21-488
HFD-580
HFD-580/A.Jordan/H.Handelsman/K.Raheja
N21488.000/5-24-2002

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):
Studies reviewed within this submission: Three non-clinical non-GLP studies with toxicologic endpoints
Studies not reviewed within this submission: studies reviewed under NDAs 21-343 and 21-379
Introduction and drug history: As stated under Overall Summary and Evaluation

TABLE OF CONTENTS

PHARMACOLOGY:

Following 3 non-GLP studies with toxicological endpoints were conducted by .

1.ATRS-289: Efficacy evaluation of leuprolide acetate released from Atrigel formulations after SC injection in rats.

2. ATRS-445: The effect of leuprolide acetate released from two Atrigel formulations of different inherent viscosities over 156 days in dogs.

3. ATRS-364: Determination of the injectability of the 120-day Atrigel formulations containing leuprolide acetate when administered subcutaneous in pigs. Final report.

Experiment schedule and results of the above studies are given in table below:

Species/ strain	# animals per g/s	Route/ No. doses	Test article	Dose & Volume	duration	Results	Study #
Rat/SD	5 M	SC x 1	Eligard 30 mg (15kD polymer MW) Eligard 30 mg (26kD polymer M.W) + 6 other formulations	12 mg/kg in 0.06ml 12 mg/kg in 0.06 ml 9 mg/kg in 0.04ml	132 day	No overt or injection site toxicity were observed over the course of the study. Serum testosterone was suppressed from Day 14 through Day 132 in both Eligard 30 mg groups.	ATRS-289 129.285)
Dog/ Beagle	6M	SC x 1	Eligard 30 mg (18kD polymer MW) Eligard 30 (23kD polymer MW)	30 mg in 0.5 ml 30 mg in 0.5 ml	156 days	No overt toxicity, no body weight changes and no injection site toxicity observed during a 28-day observation period after injection. Serum testosterone was suppressed from Day 21 through Day 135.	ATRS-445 129.411)
Pig	2F	SC	2 injections	Eligard 30 mg in 0.5 ml	3 days	No overt toxicity was observed. Slight erythema at 6 of 8 sites reported in one animal.	

Primary pharmacodynamics: see review of NDA 21-343
Secondary pharmacodynamics: see review of NDA 21-343

Pharmacology summary: Eloigard 30 mg did not result in any injection site toxicity and it suppressed testosterone to castrate levels in both rats and dogs.

Pharmacology conclusions: Eligard 30 is therapeutically effective for the 4 months.

SFETY PHARMACOLOGY:

See review of NDA 21-343

PHARMACOKINETICS/TOXICOKINETICS:
See review of NDA 21-343
TOXICOLOGY:
See review of NDA 21-343

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				

Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

GENETIC TOXICOLOGY:
See review of NDA 21-343

CARCINOGENICITY:
No carcinogenicity studies have been conducted with Eligard 30

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:
No reprotoxicity studies have been conducted with Eligard 30

SPECIAL TOXICOLOGY STUDIES:
None submitted
ADENDUM TO REVIEW:
(if necessary)

APPENDIX/ATTACHMENTS:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Krishan L. Raheja
6/3/02 11:33:06 AM
PHARMACOLOGIST

Alexander W. Jordan
6/11/02 03:13:22 PM
PHARMACOLOGIST

Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg
Atrix Laboratories, Inc.
NDA 21-488

Statistical Review of Carcinogencity Studies

Not required.

OWR 2/11/03

Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg
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CAC/ECAC Report

This new drug application was not the subject of a CAC/ECAC report.

OWR 7/11/03